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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,466	10/27/2006	Maria Teresa Flores	14829-003US1 F/USP288389	5995

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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
01/04/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/564,466	FLORES ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,19-22,25,27-32 and 34-39* is/are pending in the application.

4a) Of the above claim(s) *1-6,8-10,12,20,21,25 and 27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,11,19,22 and 34-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/22/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/15/10 has been entered.

Applicants' Amendment and Remarks, filed 10/15/10 have been entered. Claims 1-12, 19-22, 25, 27-32, 34-39 are pending; claims 1-6, 8-10, 12, 20, 21, 25, 27-32 are withdrawn; claims 7, 11, 19, 22, 34-39 are under current examination.

Information Disclosure Statement

Applicants' IDS, filed 11/22/10, has been considered.

Election/Restrictions

Applicant's election with traverse of Group II (claims 7, 11, 13-19 and 22) in the reply filed on 6/16/09 is acknowledged. Applicants continue to traverse the restriction requirement. In particular, Applicants argue that the pending claims share a technical feature, which is reverse-immortalized human OEG cells and that contrary to assertions of the office, this feature is a special technical feature for the reasons provided previously. Applicants argue that the Office reconsider the restriction requirement and cite several passages of the MPEP in support. In particular, MPEP §1850 and 37 CFR 1.475(b)(3). In particular, Applicants argue that the Office's apparent interpretation of certain passages within the MPEP appear to run afoul of PCT Rule 13.3 which states that the determination of Unity of Invention is not affected by the manner of claiming, and that the pending claims

are unified and therefore should be examined in concert. See pages 11-15 of the Response.

The Examiner responds firstly that the Restriction requirement has been made final in the prior Office action. Additionally, Applicants' arguments are with regard to whether an invention has unity of invention. In the instant case, the Examiner has provided sufficient guidance to show that unity of invention is not present, because the claimed invention does not make a contribution over the prior art. That is, the technical feature of the claims is considered to be reverse-immortalized human OEG cells, but this technical feature is not considered to be a *special* technical feature, because it does not make a contribution over the prior art of Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002), which is found below. MPEP §1850 (II) states that, "Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature," should be considered with respect to novelty and inventive step." The Examiner has provided guidance with regard to why the instant claims do not make a contribution over the prior art, and therefore, do not have a special technical feature. Thus, given that unity of invention does not exist, the claims do not form a single general inventive concept. 37 CFR 1.475 (b) relates to categories of invention that are considered to have unity of invention. In the instant case, because unity of invention is found to be lacking, these categories do not apply to the instant case.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-6, 8-10, 12, 20, 21, 25, 27-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/16/09.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7, 11, 19 and 34-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002).

Applicants' Arguments. Applicants provide the definitions of a reverse-immortalized cell and a reversibly-immortalized cell. In particular, a "reverse-immortalized" cell is one that exists in a non-immortalized state, which is directly obtained from the "reversibly immortalized" cells by subjecting to a further step of genetic modification. Thus, Applicants argue that the instant claims relate to reverse-immortalized cells, which Applicants have found retain their biological function (see pages 10-11 of the Response).

Applicants argue that the rejection states that the combination of art arrives at producing reversibly-immortalized (not reverse immortalized) OEG cells (see p. 11, last ¶ of the Response). Applicants state that Barnett teaches OEG cells but makes no mention of reverse immortalized cells. Applicants argue that Salmon discloses making reversibly-immortalized cells using excisable lentiviral vectors; Salmon teaches immortalizing human liver sinusoidal endothelial cells and pancreatic cells which are not OEG cells. Salmon teaches Cre-mediated excision of the proviral integrants but does not teach the phenotypic or functional characteristic of the reverse immortalized cells, beyond saying that they can survive up to 2 weeks (see p. 12, last ¶). Applicants argue that Salmon never characterizes the reverse-immortalized cells, and that Applicants disagree with the Office's characterization of Salmon, because Salmon states that following Cre excision, complete growth arrest is observed, but does not teach the phenotype of the markers in the deimmortalized cell line, and that Examiner's citation of the passage on p. 408, lines 4-8 refers to the reversibly immortalized cell line, not the reverse immortalized cell line. See p. 13 of the Response. Applicants further point to Salmon, and state that there are comments that would lead one to reasonably conclude that not all cell types would retain their functional properties following immortalization-deimmortalization; and in fact, Salmon indicates that functional properties can be lost after the initial step of immortalization, pointing to pages 404 and 412-13 of Salmon. Applicants argue that Salmon does not teach that reverse immortalized hLSEC are biologically functional, provides sufficient guidance and with a reasonable expectation of success that any reverse human immortalized cell would retain the characteristics of the parent cells, let alone CNS cells. All that a skilled person would learn from Salmon is that hLSEC cells can be reversibly immortalized using a lentivirus vector system, and that the skilled person would not have any reasonable expectation of success that human cells, let alone CNS

cells, could be reverse immortalized and retain their biological function. See p. 14, 1st ¶.

Response to Arguments. These arguments have been fully considered, but are not persuasive. With regard to Salmon at p. 404 and 412-13, the Examiner notes that the citation on p. 404 refers to murine primary cells. Salmon teaches that reversible immortalization in murine cells is distinct from human cells because mouse cells are easy to obtain through expression of a single oncogene. Salmon specifically addresses that human cells require specific requirements, and that one major hurdle is the failure of cells to readily divide in culture (see p. 405, col. 2, 1st full ¶). Thus, Applicants' citation of Salmon at p. 404 is not relevant to the instant invention because this passage discusses murine, not human cells. Furthermore, Salmon does not provide any guidance with regard to which phenotypic characteristics of murine cells or lost, or how this pertains to human cells. Given that murine cells do not require the specific manipulations that are recited in Salmon, this passage does not provide any guidance for an unreasonable expectation of success of using Salmon's methods in human cells, and in particular, with human OEG cells. Applicants appear to be arguing that Salmon's lack of characterization of their reverse immortalized cells suggests that their cells may not maintain the characteristics of the original, parental cells. In fact, Salmon teaches that an immortalization procedure that is reversible requires the production or function of the proteins responsible for triggering cell division be repressible (see p. 405, col. 1). Salmon presents the solution to this problem by showing the ability to transduce cells irrespective of their proliferation status, and that upon Cre expression complete growth arrest is observed, and nondividing cells survived for up to 2 weeks (p. 405 , col. 2, bridging ¶). Salmon further teach that when the tranduced cells had the transgene excised, the morphology of the cells was not fundamentally altered (p. 411, col. 1, 1st ¶). Thus, Salmon provides guidance that excision of the transgene does not change the morphological characteristics of the

cells. Moreover, at page 412, Salmon states that during immortalization, specific traits of the parent may be lost during the growing phase, but restored after "deimmortalization." Further, "Our results with human muscle cells support this contention, by showing that the fusion score of immortalized myoblasts increased dramatically after excision of the growth-promoting genes." See p. 412, col. 2, ¶2. Thus, Salmon, contrary to teaching unpredictability or teaching away from reversible-immortalization, suggest that any loss of phenotype is restored upon excision of the transgene.

Applicants have not provided any guidance that using the methods described in the combined art, one of skill would have had an unreasonable expectation of success in achieving a population of reverse-immortalized human OEG cells. In contrast, Salmon shows that there is no morphological change in their resultant, excised cell line, and further, that any phenotypic changes are likely to be restored upon deimmortalization (*i.e.*, excision of the transgene). One of skill in the art, reading Salmon, would recognize that their immortalization techniques could readily, and without undue experimentation, be applied to any type of cell, including OEG cells.

Applicants' Arguments. Applicants argue that Halfpenny reviews experimental myelin repair of different glial cells in disease, such as multiple sclerosis, but they do not consider the ability of promote axonal regeneration of these cells, and thus, the skilled artisan would not expect that immortalized glial cells, such as those described in Halfpenny, would be suitable to promote axonal regeneration after transplantation. See p. 14 of the Response. Applicants argue that Halfpenny acknowledges that there are difficulties with producing human cells that are reversibly immortalized and are not faithful to their parent cells (at p. 34).

Response to Arguments. These arguments have been considered but are not persuasive. Applicants' arguments regarding Halfpenny's teachings have been fully considered but are not persuasive. In particular, the passage which Applicants cite

has been taken out of context. Halfpenny do not teach or suggest that the immortalized glial cells would not be suitable to promote axonal regeneration after transplantation, because the skilled artisan would not have any expectation of repair or regeneration where axonal loss already exists. Rather, Halfpenny teach that the timing of remyelinating treatment is important, because early intervention may offer a significant advantage. Halfpenny do not explicitly or implicitly teach away from using immortalized glial cells to promote axonal regeneration, they merely caution about the time frame in which to use the cells in transplantation.

Regarding Applicants' citation of Halfpenny at p. 34, Halfpenny discusses OPC cells (*i.e.*, oligodendrocyte progenitor cells), but do not specifically discuss OEG cells. Additionally, although Halfpenny states that some glial cell lines are not faithful to their primary cells, Halfpenny does not provide guidance as to what characteristics are not faithful, and additionally, which cell types. Halfpenny does not specifically discuss unpredictability in OEG cells in the passage cited by Applicants. Halfpenny is used with regard to motivation to produce reversibly-immortalized cells. The teachings of Barnett and Salmon provide sufficient teachings, guidance and motivation such that one of skill in the art would arrive at the claimed invention.

It is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A)

Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

In the instant case, one of ordinary skill in the art, reading Barnett and Salmon, would readily recognize that reverse-immortalization is a known technique by the skilled artisan. Additionally, Salmon's teachings show that reverse-immortalization can be applied to various human cell types with success. Given that the art teaches that some of the phenotypic traits that are lost upon immortalization can be restored after re-immortalization (see Salmon at p. 412, col. 2, ¶2), and that Halfpenny provide sufficient motivation to make such reversible-immortalized cells, it is maintained that the combination of Barnett, Salmon and Halfpenny provide a reasonable expectation of success, with sufficient motivation and guidance to arrive at the claimed invention.

Rejection

Barnett teach the isolation and identification of human olfactory ensheathing glial cells (p. 1582, col. 1, Isolation and Culturing of human OECs). Barnett teach the purification of the human OECs (p. 158, 2nd col., Purification of hOEC using L-

NGFr and Magnetic Beads). Barnett teach that cells are capable of remyelinating persistently demyelinated CNS axons following transplantation into rat spinal cord (Abstract).

Barnett do not teach that their cells are reversibly immortalized. However, prior to the time of the claimed invention, Salmon teach the reversible immortalization of human primary cells by lentivector-mediated transfer. In particular, Salmon teach utilizing a vector comprising the SV40 large T (Tag) oncogene (Abstract).

Regarding newly added embodiments of claims 34-35, Salmon teach a construct that contains LoxP sites, and that the cells were treated with Cre recombinase (Abstract, Figure 1A, *Vectors and Plasmids*, p. 408, col. 1-2). Regarding claims 36 and 39, Salmon teaches a vector that contains the SV40 large T antigen or human telomerase catalytic subunit (hTERT) (p. 408, *Vectors & Plasmids*). Regarding claims 37-38, Salmon teach that the vector contains thymidine kinase (p. 409, col. 1, Design of Excisable Lentiviral Vectors) and that the cells are sensitive to ganciclovir (p. 409, col. 1, Excision of the Transgene and Conditional Ablation of Unexcised Cells).

Accordingly, in view of the combined art of Barnett and Salmon, it would have been obvious for the ordinary skilled artisan to modify the OEG cells, taught by Barnett, to produce reverse immortalized OEG cells, utilizing the methods of Salmon, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to produce reversibly-immortalized OEG cells in order to produce a large number of therapeutic cells for transplantation, as suggested by Salmon (p. 404, Introduction) and further specifically suggested by Halfpenny who teach immortalized cell lines would provide sufficient numbers of cells for transplantation, which could yield large numbers of appropriate cells in homogeneity. See p. 34, col. 2, Immortalised Cell Lines.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 22 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002) as applied to claims 7, 11, 19 and newly added claims 34-39 above, and further in view of Franklin *et al.* (**Glia**, 17: 217-224, 1996). The prior rejection of claim 18 is rendered moot in view of the cancellation of the claim.

Applicants' Arguments. Applicants provide the same arguments regarding Barnett, Salmon and Halfpenny. These arguments are addressed above. Applicants argue that Franklin describes the use of a retrovirus containing the ts mutant gene of the Tag, but do not excise the oncogene because they argue that the immortalizing gene product is not active following transplantation into the rat. Applicants argue that nevertheless, it is explained in the present Application that the continued presence of the oncogene in these cells is of concern because it may increase the risk of malignant transformation following transplantation. Applicants argue that one of ordinary skill in the art would not have been motivated to obtain a clonal-reverse immortalized human OEG cells with expectation of success and enough safety to further transplant into humans, utilizing the teachings of Franklin, in combination with Barnett, Salmon and Halfpenny. See page 17 of the Response.

Response to Arguments. Applicants' arguments with regard to Franklin are not found to be persuasive. In particular, Franklin is not relied upon with regard to the specific vector they use. Franklin is used with regard to the production of an OEG line. The combined teachings of Barnett, Salmon and Halfpenny provide guidance with regard to the excision of the oncogene.

Rejection

Barnett, Salmon and Halfpenny are discussed above. They do not specifically teach an OEG cell line. However, prior to the time of the claimed invention, Franklin teach the generation of olfactory bulb ensheathing cell lines (p. 218, col. 1, Materials and Methods, Construction of the tsT OBEC Cell line and verification of Clonality).

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art to utilize the teachings of Barnett, Salmon and Halfpenny, to produce a reverse-immortalized human OEG cell culture, and then utilize the teachings of Franklin, in order to produce a clonal reverse-immortalized human OEG cell line, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make a cell line in view of Franklin's teachings, who state that, "The reason for using a cell line rather than cells derived from primary culture is that it is difficult to obtain pure populations of the latter that are free from any contaminant phenotype." See p. 218, col. 1, 1st full ¶.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632